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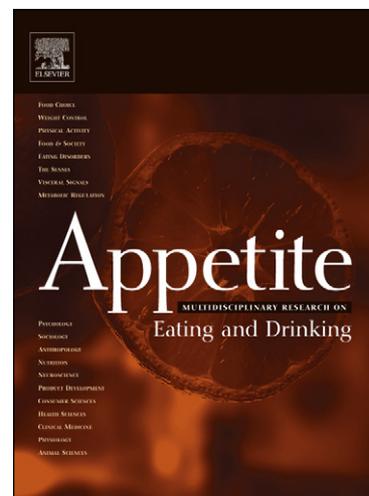
Acute neurocognitive effects of epigallocatechin gallate (EGCG)

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Abstract

Green tea is reported to have wide ranging beneficial health outcomes across epidemiological studies, which have been attributed to its flavonoid content. We investigated whether the flavonoid epigallocatechin gallate (EGCG) modulates brain activity and self-reported mood in a double-blind, placebo controlled crossover study. Participants completed baseline assessments of cognitive and cardiovascular functioning, mood and a resting state electroencephalogram (EEG) before and then 120 minutes following administration of 300 mg EGCG or matched placebo. EGCG administration was associated with a significant overall increase in alpha, beta and theta activity, also reflected in overall EEG activity, more dominant in midline frontal and central regions, specifically in the frontal gyrus and medial frontal gyrus. In comparison to placebo the EGCG treatment also increased self-rated calmness and stress. This pattern of results suggests that participants in the EGCG condition may have been in a more relaxed and attentive state after consuming EGCG. This is in keeping with the widespread consumption of green tea for its purported relaxing/refreshing properties. The modulation of brain function due to EGCG is deserving of further controlled human studies.

Introduction

Over the past decade or so, there has been growing interest in the potential health benefits associated with the consumption of flavonoid-containing foods, including those which may have implications for cognitive function. Flavonoids are a diverse class of natural compounds, which are ubiquitous within plants. Several subcategories predominate, including flavonols, isoflavones, flavones, flavanones, and anthocyanidins (Aron and Kennedy 2008). Among the dietary flavonoids, high levels are found in numerous common food stuffs such as grapes, red wine, apples, cocoa and both black and green tea (Gu et al. 2004). They are abundant in green tea, primarily as catechins, including epicatechin (EC), epigallocatechin (EGC), epicatechin gallate (ECG) and epigallocatechin gallate (EGCG) (Cabrera et al. 2006). EGCG is the most abundant catechin found in green tea, accounting for around a third of the solid content (Potenza et al. 2007) and 65% of the total catechin content (Zaveri 2006). A typical cup of green tea contains approximately 150-200mg total flavonoids of which 90-100mg are catechins (Hodgson and Croft 2010). The high catechin content of green tea may underlie its reported health benefits in relation to oral health, weight management and preventive effects against a number of chronic conditions including cardiovascular disease, cancer and neurodegenerative disease (Adak and Gabar 2011). Meta-analyses of population studies concerning tea (black or green) consumption suggest that drinking three cups of tea a day reduces the chances of myocardial infarction by 11% (Peters et al. 2001), and reduces the risk of ischemic stroke by 21% (Arab et al. 2009). Of particular relevance to this study is a modest but significant association between green tea consumption and lower psychological distress (Hozawa et al. 2009).

Pre-clinical *in vitro* and *in vivo* studies indicate a variety of benefits relevant to human brain functioning attributable to green tea polyphenols (Chen et al. 2009). The neuroprotective

effects of EGCG have been demonstrated in regards to its ability to effect cell survival and signal transduction in models of neurotoxicity (Bastianetto et al. 2006), ischemia (Lee et al. 2004), Parkinson's disease (Kang et al. 2010; Tai and Truong 2010) and Alzheimer's disease (Lee et al. 2009; Rezai-Zadeh et al. 2008). As well as these cross-sectional and pre-clinical studies, dietary intervention trials have demonstrated that the consumption of green tea can improve endothelial function (Heiss et al. 2003), while the mechanisms underlying these effects remain to be elucidated, they may be related to changes in the pool of bioavailable nitric oxide (NO) (Fisher et al. 2003). Flavonoid administration leads to replenishment of endothelium-derived NO stores, leading to better systemic cardiovascular function and vaso-protective effects (Hodgson and Croft 2010). Studies have shown that cocoa (a substance rich in flavanols) offers protection for the vascular endothelium by improving NO availability (Heiss et al. 2003). Research into the potential neurocognitive effects of flavonoid extracts have produced mixed results. Administration of cocoa polyphenols over a period of days increased brain activation and cerebral blood flow, but did not improve cognitive functioning (Crews Jr et al. 2008; Francis et al. 2006). To date only one study has identified acute enhancement of cognitive function from polyphenols, with cocoa flavanols improving performance on mentally effortful cognitive tasks 90-150 min post-ingestion (Scholey et al. 2010). Administration of the red wine flavonoid resveratrol had no influence on performance of the same task (Kennedy et al. 2010), but did increase cephalic blood flow as measured using Near Infrared Spectroscopy.

The above evidence suggests that the effects of flavonoids on neural activation can be dissociated from their behavioural effects. Additionally given the well-documented acute effects of green tea, and EGCG in isolation on cardiovascular functioning (Hodgson and Croft 2010), we hypothesised that EGCG would acutely modulate brain bioelectrical activity and behaviour. The current double-blind, placebo-controlled, crossover study therefore investigated the effects

of a single 300 mg dose of EGCG on brain activity and mood measured post-administration. We

chose this dose as it has been shown to acutely improve endothelial function 2 h post-

administration (Widlansky et al. 2007). Electroencephalography (EEG) has been used

successfully to capture psychopharmacological effects (Fink 2010; Itil et al. 1998; Saletu et al.

2010) and the effects of several nutritional interventions including components of tea (Kelly et

al. 2008; Nobre et al. 2008).   Given the wide range of potential brain relevant parameters that

might be modulated by EGCG consumption, we opted to use EEG, which has excellent

(millisecond) temporal resolution and relatively good spatial resolution in order to initially

capture any acute effects of EGCG on brain activity.

Methods and Materials

Subjects

Thirty-one volunteers (mean age 27.74yrs, SD 9.28; 12 males, 19 females) completed the

study which was approved by the Swinburne University Human Research Ethics Committee and

conducted in accordance with the Declaration of Helsinki. All participants were non-smokers,

normal weight (mean weight 71.4 kg, range 46 - 95), right-handed, English speaking, not taking

illicit drugs, medications or natural therapies, and free of psychological (e.g., depression,

anxiety) or physical conditions (food allergies, kidney disease, liver disease and/or

gastrointestinal diseases) that would affect food metabolism.

Treatment

The trial treatment Teavigo® is a caffeine-free purified and refined extract of *Camelia*

sinensis consisting of approximately 94% EGCG, and 6% Vitamin C (ascorbyl palmitate derived

from corn dextrose fermentation and palm oil) and hypo-allergenic plant fiber derived from pine

cellulose. Several studies have confirmed Teavigo® as safe for human consumption (Widlansky

et al. 2007), with no study identifying any adverse side effects at the dosage implemented in the current study (300mg). The placebo treatment was an identical capsule containing flour. Participants were asked to refrain from caffeinated products from midnight the night prior to study visits. Following a familiarity period where measures were demonstrated to participants, each was randomly allocated either treatment at the first visit, and returned one-week later to complete a second testing session. Testing sessions began at 10.00 or at 14.00 (at the same time for each participant's two study visits) and consisted of a series of measures at baseline which were repeated following placebo and EGCG consumption (with treatment order counterbalanced). The assessments consisted of measures of cognitive and cardiovascular functioning (which will be presented elsewhere) then, beginning 180 mins following consumption, mood and resting state EEG which are reported herein. These timings were chosen to optimise the chances of capturing any acute effects of EGCG, with pharmacokinetic studies showing peak absorption between 1.6 and 3.2 h and a mean elimination half-life of 2.5 h (Manach et al. 2005).

Electrophysiological Measures & Analyses

The EEG was recorded with a 40 channel Neuroscan NuAmp EEG system. All scalp electrode impedances were kept below 5 kΩ and were referenced via both mastoid bones and grounded via the cap. Vertical eye movements were monitored with electrodes placed directly below the left eye, and horizontal eye movements were monitored with electrodes placed at the outer canthi of the right eye. Amplifiers were set with a gain of 5000, with a band-pass of 0.01-100 Hz and a sample rate of 256 Hz. EEG was recorded during all double blind pre-dose and post-dose conditions for eyes closed and eyes open. Each condition consisted of two minutes of recording. Using the analysis program BrainVision Analyser (Brain Products, 2008), ten seconds of artefact free EEG spectral activity associated with eyes open and eyes closed were analysed

and absolute power for each bandwidth was calculated (Gevins and Cutillo 1986) and corrected for EOG (Gratton et al. 1983). A grand average for each session and condition was calculated. A further band-pass filter of 0-30Hz was implemented to the final average. Change-from-baseline values were then compared for both placebo and EGCG. A topographical T-test on EEG data associated with pre and post effects associated with placebo and EGCG were constructed for changes in EEG power across the 10 second epochs of EEG for each condition and normalised grand average. Significance and P values for the differences for overall activity were calculated and converted into topological probability maps using BrainVision Analyser 2.0 (Brain Products, 2008). Low Resolution Brain Electromagnetic Tomography (LORETA) analyses; a source localisation technique to determine the sources of activity associated with scalp EEG (Pascual-Marqui et al. 1994), was implemented to further validate the source of the topographical distribution of band activity (theta, alpha, beta) observed.

Mood: visual analogue mood scales

The Bond–Lader mood scale (Bond and Lader 1974) is made up of 16×100 mm visual analogue mood scales (VAMS) with the end-points anchored by antonyms. Participants were presented with a sheet of paper containing the scales and instructed to mark their current mood state on each line. Three mood measures are derived, with scores on each ranging from 0 to 100: 'alertness' (from individual VAMS of alert-drowsy, attentive-dreamy, lethargic-energetic, muzzy-clearheaded, well-coordinated-clumsy, mentally slow-quick witted, strong-feeble, interested-bored, incompetent-proficient); 'calmness' (calm-excited, tense-relaxed); and 'contentedness' (contented-discontented, trouble-tranquil, happy-sad, antagonistic-friendly, withdrawn-sociable). Additionally two single VAMS were presented as 100 mm lines labelled 'stress' and 'fatigue' with the endpoints marked 'not at all' and 'extremely' respectively.

Results

T-tests comparing group change-from-baseline scores revealed that, compared with placebo, EGCG treatment significantly increased calmness, $t(29) = 2.17$, $p = .04$) and reduced stress, $t(29) = 2.52$, $p = .017$, (see Figure 1a). No other treatment effects were significant.

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Figure 1 around here

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Artefact-free EEG spectral activity associated with eyes open and eyes closed were analysed and absolute power for each bandwidth was calculated. Compared with placebo, EGCG administration was associated with a significant overall increase in alpha, beta and theta activity (data not shown), more dominant in midline frontal and central regions. These data are summarised in Figure 1b (where warmer colours represent greater activity across all bandwidths).

LORETA analyses; a source localisation technique to determine the sources of activity associated with scalp EEG, was implemented to further validate the source of the topographical distribution of bioelectrical activity. LORETA analysis confirmed that this pattern of activation was associated with frontal sources located in the frontal gyrus and medial frontal gyrus, corresponding to Brodmann areas 6 and 10 respectively (see Figure 1c and 1d).

Discussion

The improved ratings of calmness and stress in conjunction with the EEG results described below reflect a pattern that is largely consistent with the widely-reported anecdotal effects of tea drinking – that consuming either black or green tea is both relaxing and alerting.

The most striking results were in the EEG facet of the study where we found increased activity in EEG across all bandwidths. LORETA analysis localised the source of this activation to regions implicated in high level integration of information stemming from visual, auditory, and somatic sensory systems to achieve amodal, abstract, conceptual interpretation of the environment (Wood and Grafman 2003). Similar patterns were observed when LORETA was applied to individual wavebands (data not shown), though such filtering inevitably results in loss of information. Our approach is consistent with other studies where larger bandwidths are used (e.g. Saletu et al. 2010).

Resting human theta activity is primarily associated with quiet wakefulness (Cantero et al. 2003), beta activity is attenuated by movement and increases with behavioural arousal and focused attention and alpha activity is characterized by large rhythmic waves that are associated with relaxation and the lack of active cognitive processes. Previously, an increase in both alpha and theta activity has been observed during non-directed meditation (Lagopoulos et al. 2009), which the authors interpret as resulting from a relaxed state or mindfulness. We would speculate that the changes in these same waveforms in the EGCG condition may reflect a relaxed yet attentive state due to the intervention. Future studies could usefully be directed at examining EEG patterns while engaging in cognitive tasks.

Previous research concerning alterations in EEG activity following black tea consumption has shown that the amino acid theanine (-N-ethylglutamine) alters brain activity associated with attentional functioning (Kelly et al. 2008) and increases feelings of calmness and relaxation (Nobre et al. 2008) similar to the current findings relating to acute EGCG administration. It

would be of interest to directly compare separate and combined effects of EGCG and theanine using the methodology from the present study. It is worth noting that the effects here are somewhat different to those reported for black tea where acute improvements to attention were found; along with improved ratings of alertness on the same Bond-Lader VAMS used here (De Bruin et al. 2011). Black tea contains no EGCG (which is oxidised to thearubigin during the fermentation process), suggesting that a different profile of flavonoids, or indeed other components may differentiate the behavioural effects of green and black tea.

Growing evidence from *in vitro*, *in vivo* and randomized controlled human studies supports the notion that green tea consumption can improve endothelial function (Hodgson and Croft 2010) through actions of the flavonoids (specifically EGCG) found in green tea. Although the parent molecule ECGC itself has relatively low bioavailability, recently EGCG has been observed to improve endothelial function in humans via enhancement of NO status (Widlansky et al. 2007). Given the wide range of effects attributed to NO in the central and peripheral nervous system and normal brain functions such as memory and learning, this mechanism seems most plausible for the results reported herein.

This study is the first to report the effects of EGCG on brain activity and mood utilizing a double-blind, placebo controlled, randomized cross-over design. With tea being the most widely consumed beverage in the world, apart from water (Shen and Chen 2008), the contribution of green tea's predominant flavonoid EGCG towards brain function is of growing interest. Further studies are needed to clarify the acute effects of EGCG supplementation in dose-ranging studies and in comparison to actual green tea consumption to ascertain what dosing regimen is of greatest benefit to short and long term mental functioning.

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Figure legend

<u>Figure 1</u>

Effects of EGCG compared with placebo on mood and EEG activity. **a.** shows significant differences between placebo and EGCG change-from baseline scores (* p < .05). **b.** depicts change from baseline in overall EEG activity associated with placebo and EGCG, warmer colours represent more significant differences between treatments (probabilities shown in the key).   **c.** and **d.** depict LORETA source localisation of EEG activity associated with EGCG, where each brain image depicts a superior, sagittal view and coronal view associated with the EEG sources for the post dose EGCG for two counterbalanced sessions.

Figure(s)

a)

b)

PLACEBO   EGCG

c) <u>Brodmann Area 10</u>
Mid Frontal Gyrus

d) <u>Brodmann Area 6</u>
Frontal Gyrus/
Medial Frontal Gyrus